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The Developmental Consequences of Low to Moderate Prenatal and Postnatal Lead Exposure: Intellectual Attainment in the Cincinnati Lead Study Cohort Following School Entry

KIM N. DIETRICH,*[1] OMER G. BERGER,† PAUL A. SUCCOP,*
PAUL B. HAMMOND‡, AND ROBERT L. BORNSCHEIN*

*The University of Cincinnati College of Medicine, Department of Environmental Health and Division of Epidemiology and Biostatistics, Cincinnati, OH 45267-0056
†The Children's Hospital Medical Center of Cincinnati and University of Cincinnati, College of Medicine, Department of Pediatrics, Cincinnati, OH 45267-0054
‡The University of Cincinnati College of Medicine, Department of Environmental Health, Division of Toxicology, Cincinnati, OH 45267-0056

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DIETRICH, K. N., O. G. BERGER, P. A. SUCCOP, P. B. HAMMOND AND R. L. BORNSCHEIN. *The developmental consequences of low to moderate prenatal and postnatal lead exposure: Intellectual attainment in the Cincinnati Lead Study Cohort following school entry.* NEUROTOXICOL TERATOL 15(1) 37–44, 1993.—In a further follow-up study of the Cincinnati Lead Study Cohort, 253 children were administered the Wechsler Intelligence Scale for Children-Revised (WISC-R) at approximately 6.5 years of age. Postnatal blood lead concentrations were inversely associated with Full-Scale (FSIQ) and Performance IQ (PIQ). Following statistical adjustment for developmental co-factors such as maternal IQ and an assessment of the quality of caretaking in the home environment, a statistically significant relationship remained between postnatal blood lead concentrations and PIQ. Further statistical analyses suggested that averaged lifetime blood lead concentrations in excess of 20 μg/dL were associated with deficits in PIQ on the order of approximately 7 points when compared to children with mean concentrations less or equal to 10 μg/dL. These results are discussed in terms of their consistency with other similar studies as well as their internal consistency with earlier reports on this cohort. The findings of this investigation support recent initiatives in the United States to reduce the exposure of children to environmental lead.

Lead Children Cognitive-development Epidemiology

PB-11928

IN AN OCTOBER, 1991 address, Dr. Louis Sullivan, Secretary of Health and Human Services called lead (Pb) ". . . the number one environmental threat to the health of children in the United States" (23). In a written introduction to the latest statement on this environmental issue by the United States Centers of Disease Control, Pb poisoning is referred to as "one of the most common and preventable pediatric health problems today" (24; p. 1). Although these statements by regulatory agencies and their spokespersons carry a substantial degree of certitude, controversy remains in the scientific community as to whether lead exposures which do not produce frank symptoms are nevertheless associated with subtle functional or physiological deficits (i.e., abnormal patterns of development in behavior, intellect, or physical growth (12).

Even more uncertain are the long-term implications of early lead exposure, including exposures to Pb which can occur in utero. Recent prospective studies of pediatric Pb exposure seem to have demonstrated that the adverse neurobehavioral effects of prenatal exposure (as indexed by the concentration of Pb in maternal or cord blood) are transient, particularly in the absence of higher postnatal exposures (2,3,6,16). However, the Cincinnati prospective study continued to report

[1] To whom requests for reprints should be addressed.

a significant inverse association between neonatal PbB concentrations and behavioral performance at 4 and 5 years of age (7,8). Furthermore, a recent examination of the relationship between the concentration of Pb and other heavy metals in amniotic fluid and preschool neurobehavioral deficits has produced positive findings (14).

There are only a few published accounts of the effects of early lead exposure on later school-age intellectual attainment. A group of investigators in Boston have periodically reported on a cohort of children from Chelsea and Somerville, MA (18,20). Neurobehavioral and academic performance deficits associated with the amount of Pb in dentin were found from the first grade through high school. As high school students, young adults who were earlier identified with higher levels of Pb in dentin were more likely to present with a reading disability and fail to graduate (20).

Among the prospective studies initiated at the start of the last decade, only the one conducted in Boston has reported on the effects of early Pb exposure on later school age intellectual and academic achievement (3). The investigators described the continued presence at age 10 years of a statistically significant, inverse association between a child's PbB concentration at 24 months and cognitive and academic functioning. Such a finding is particularly interesting given the low concentrations of Pb in blood at 2 years ($M < 7$ μg/dL). Over the range of approximately 0 to 25 μg/dL and following statistical adjustment for covariates, a 10 μg/dL increase in PbB concentration at 2 years of age was associated with a 6-point decline in IQ and a 9-point decline in a similarly standardized academic performance composite score (i.e., a Pb-associated drop of approximately one-half SD in intellectual and academic performance).

In another prospective study being conducted in the vicinity of a longstanding Pb smelter in Port Pirie, South Australia, a 4- to 5-point drop in the IQ of about 500 7 year olds was observed in association with an increase in lifetime average PbB levels from 10 to 30 μg/dL (17). This association was statistically significant after adjustment for a large number of biomedical and socio-hereditary cofactors.

This article reports on the results of neurobehavioral studies conducted on 253 children from the Cincinnati Prospective Study at 6.5 years of age. We have previously described the results of cognitive developmental testing at 4 and 5 years of age (7,8). This article represents a longitudinal extension of our ongoing work.

METHOD

Subjects

Details of the procedures for subject recruitment and eligibility criteria can be found in our earlier reports (7-8). The sociodemographic and biomedical characteristics of this predominantly African-American, inner-city cohort have also been previously presented[2](7). A total of 253 subjects were available for analysis at age 6.5 years. Four subjects were excluded from further analyses for medical conditions other than Pb poisoning (Visual handicap, $n = 1$, Tourette's Syndrome, $n = 1$, Fetal Alcohol Syndrome, $n = 1$, and Sickle Cell Anemia, $n = 1$).

The base population for this 6.5 year follow-up was the 347 subjects who were initially evaluated postnatally during the first two years of life at either 3, 6, 12, or 24 months of age. Two hundred and fifty-three subjects were examined psychologically and medically at approximately 78 months of age ($M = 78.7 \pm 2$ months). There were four sets of twins in the sample. Table 1 presents a comparison of subjects who were not assessed at this age with those in the present follow-up sample on a variety of key sociodemographic, biomedical, and exposure variables. Subjects retained in the sample did not differ from those lost to follow-up in terms of perinatal medical status, maternal age, maternal IQ, or on measures of the quality of caretaking in the home environment. When compared to children who were not evaluated developmentally, subjects in the present sample had slightly higher blood lead (PbB) concentrations in the first year of life. This protocol has been reviewed and approved by the University of Cincinnati Medical Center Institutional Review Board.

Exposure Assessment

A description of the procedures for obtaining and analyzing blood samples for Pb can be obtained from previous reports (5,7,21). Blood was collected prenatally from the mother near the end of the first trimester of pregnancy (PrePbB), at approximately 10 days from the neonate (NeonPbB), and at quarterly intervals to the age of 5 years. Blood was also sampled at 66, 72, and 78 months. A majority of postnatal blood samples were drawn by venipuncture. Contamination of blood samples drawn by a method other than venipuncture was not a problem because of thorough presampling cleansing practices. Studies comparing the results of finger stick and venipuncture methods in our laboratory have yielded no appreciable differences between the two methods when these strict practices are adhered to.

We chose to express postnatal Pb exposures as the mean PbB concentrations of the 1st through 6th year of life (MeanPbB1-6) Average lifetime blood Pb level was defined as the mean of 20 quarterly PbB assessments and the PbBs at 66 and 72 months of age (MPbBLife). As previously observed (7), study results did not vary as a function of exposure characterization (e.g., mean vs. peak PbB).

Neurobehavioral Assessment

The primary developmental endpoints in this report are the Full Scale IQ (FSIQ), Performance IQ (PIQ), and Verbal IQ (VIQ) as assessed by the Wechsler Intelligence Scale for Children-Revised (WISC-R; 25). Children were tested in the morning at a pediatric clinic located in the heart of the study recruitment area. All neurobehavioral testing occurred prior to the medical examination and phlebotomy. Only one experienced psychometrician was involved in testing. This is typically considered an optimal arrangement for this kind of investigation as variance due to inter-examiner differences is eliminated (9).

Assessment of Covariables and Data Analysis

A variety of covariates and potential confounders were assessed in this investigation, including measures of fetal distress and growth, perinatal complications, prenatal maternal substance abuse, postnatal indices of health and nutritional status, sociodemographic characteristics, maternal IQ, and features of the home environment known to be associated with adequate social and cognitive development. The procedures for the assessment of these cofactors are presented in previous articles (7,8).

Our data analytic strategy has been presented in detail in a previous report (5). Data analyses employed multiple linear regression statistical techniques that examined the relationship

TABLE 1

A COMPARISON OF MEAN VALUES FOR KEY SOCIODEMOGRAPHIC, PERINATAL, AND EXPOSURE VARIABLES BY FOLLOW-UP STATUS

Variable	Status	Mean	SD	t	p
Birth weight	−	3140.5	488.3		
	+	3144.5	454.2	−0.07	0.94
Gestational age	−	39.4	1.6		
	+	39.6	1.7	−0.75	0.45
Obstetrical	−	83.2	5.7		
complications score (15)	+	82.5	5.7	1.09	0.28
Postnatal	−	95.2	8.6		
complications score (15)	+	94.2	9.7	0.93	0.35
Maternal age at birth	−	22.9	5.3		
	+	22.5	4.2	0.73	0.47
Maternal IQ (22)	−	74.1	10.2		
	+	75.3	9.3	−0.81	0.42
H.O.M.E. score (4) at 2 years	−	33.3	4.9		
	+	33.2	5.6	0.16	0.87
H.O.M.E. score (4) at 3–4 years	−	33.0	6.4		
	+	32.5	6.6	0.36	0.72
Mean PbB 3–12 months	−	9.3	3.9		
	+	10.6	5.1	−2.41	0.02
Mean PbB 15–24 months	−	15.7	7.3		
	+	17.1	8.4	−1.17	0.24
Mean PbB 27–36 months	−	15.2	7.0		
	+	16.3	7.7	−0.98	0.33
Mean PbB 39–48 months	−	13.3	6.9		
	+	14.0	7.2	−0.68	0.50
Mean PbB 51–60 months	−	11.2	5.9		
	+	11.8	6.3	−0.57	0.56

Minus sign signifies no 6.5 year follow-up, a plus sign indicates that the subjects were available for examination and are in the current analyses.

between blood indices of prenatal/postnatal Pb exposure and cognitive developmental status at 6.5 years. Covariables were pretested for their confounding potential. Any cofactor associated with the primary developmental outcome variable(s) at $p < 0.15$ was considered in the multivariate regressions. Following both backward and forward elimination procedures, any cofactor still associated with developmental outcomes at $p < 0.10$ was retained in the model. Forward and backward elimination procedures yielded the same models. We also examined two potential effect modifiers, child sex, and social class. Such interactions have been observed in previous studies and in this cohort in early infancy (5) and the later preschool years (7). All p values cited in this report are two-tailed.

RESULTS

Characterization of PbB Concentrations and Cognitive Developmental Status

Descriptions of the sociodemographic and biomedical characteristics of this cohort of children and their families have appeared in earlier reports and are not duplicated here (5,7). As previously mentioned, this cohort is predominantly African-American and on some form of public assistance.

Perinatal exposure to Pb in this cohort was low. Mean PrePbB concentration in women was 8.3 μg/dL (± 3.7) and mean NeonPbB (newborn) concentration was only 5 μg/dL (± 3.4). Figure 1 presents the postnatal PbB concentration profile for the study sample from 3 to 60 months of age. Blood Pb concentrations peaked at approximately 2 years of age and gradually declined thereafter. Approximately 35% of the sample had at least one PbB concentration equal to or greater than 25 μg/dL sometime during the first 5 years of life, while 79% exceeded the current United States Centers for Disease Control action level of 15 μg/dL during the same period (24). Virtually all of the children (95%) exceeded 10 μg/dL in the first five years of life.

Correlations between postnatal PbB levels suggested that there was a considerable degree of intra-individual tracking. For example, the Pearson correlation between mean PbB levels in the first two years of life and mean PbB levels for the third and fourth years was 0.82 ($p = 0.0001$) (7). This indicates that for most children in the cohort, the relative magnitude of the PbB concentrations remained constant with increasing age. Naturally, this constancy limits the exploration of the effect of age-specific PbB concentrations on neuropsychological development, and therefore, the determination of critical or sensitive periods postnatally. Correlations between indices of prenatal exposure (PrePbB and NeonPbB) and postnatal PbB ranges from 0.25 to 0.41. These correlations may reflect a small contribution of maternal PbB to postnatal PbB concentration, and/or the fact that mother and child shared a similar physical environment.

Approximately 8% of the children were administered chelating drugs sometime during the first 6 years of life. In the majority of cases, the chelation challenge did not proceed to a

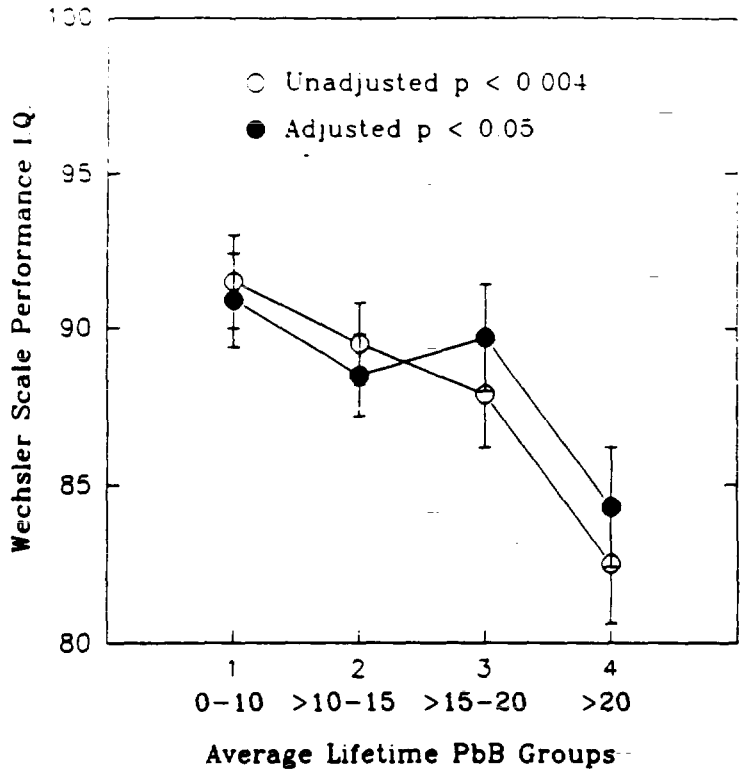

FIG. 2. Unadjusted and adjusted dose-effect relationships between average lifetime PbB concentrations and Wechsler Performance I.Q. Mean lifetime PbB concentrations and Ns within each group were as follows: Group 1, N = 68, M = 7.7 ± 1.4 μg/dL; Group 2, N = 89, M = 12.3 ± 1.4 μg/dL; Group 3, N = 53, M = 17.1 ± 1.2 μg/dL; Group 4, n = 41, M = 26.3 ± 5.0 μg/dL.

tionship between PbB category and PIQ. The difference in IQ between the lowest and highest exposure groups was approximately 9 points prior to statistical adjustment for covariates and 7 points following adjustment. It is also evident that the group with lifetime average exposures in excess of 20 μg/dL were the most compromised.

DISCUSSION

Children who experienced average lifetime exposures of 20 μg/dL or greater displayed moderate deficits in Wechsler PIQ relative to their less exposed peers. Some have argued that such effect sizes are "clinically insignificant" for any individual child. However, a drop of one-half SD related to a toxic exposure has substantial health significance when framed in the context of large populations of children. That is, one must consider the societal costs of a reduction of 7 IQ points in the total affected population (19). Thus, for example, an authority in this field has calculated the public health implications of such a phenomenon in a hypothetical population. In a group of 100 million, 2.3 million would have IQ's above 130 (i.e., very superior) assuming a population mean and SD of 100 ± 15. If the population mean IQ was shifted only 5 points to 95, the number of individuals functioning in the very superior range would drop by more than half (26). Of course, the number of individuals with IQ's below 70 (i.e., borderline or mentally deficient) would correspondingly increase.

Note that many of the children with lifetime average PbB concentrations of greater than 20 μg/dL exhibited fairly high levels of Pb in the blood at earlier ages. Figure 3 presents the mean lifetime PbB profile for this subgroup of 41 subjects. Virtually all of the subjects in this subgroup (93%) had at least one or more PbB concentration in excess of 30 μg/dL. This illustrates that caution needs to be exercised in the description of threshold phenomena when lifetime PbB concentrations are used as an index of dose.

The results of this investigation are consistent with those of at least two other major prospective studies (2,16). Studies conducted in Boston and Port Pirie, South Australia have both reported a greater effect of Pb on PIQ as compared to VIQ when children were assessed just prior to school entry. Our findings do not agree with the generally negative findings of a study of prenatal alcohol exposure and Pb reported from Cleveland (11). Our findings are internally consistent with two previous reports on the cognitive developmental status of this cohort (7,8). At 4 and 5 years of age, we consistently observed a greater effect of lead on subscales of the Kaufman Assessment Battery for Children (13) which were similar psychometrically to PIQ as measured on such scales as the Wechsler and McCarthy Scales of Children's Abilities.

The major difference between this report and previous articles is that statistical significance was retained following adjustment for such covariates as maternal IQ and H.O.M.E. scores. This may be a function of the increased reliability and

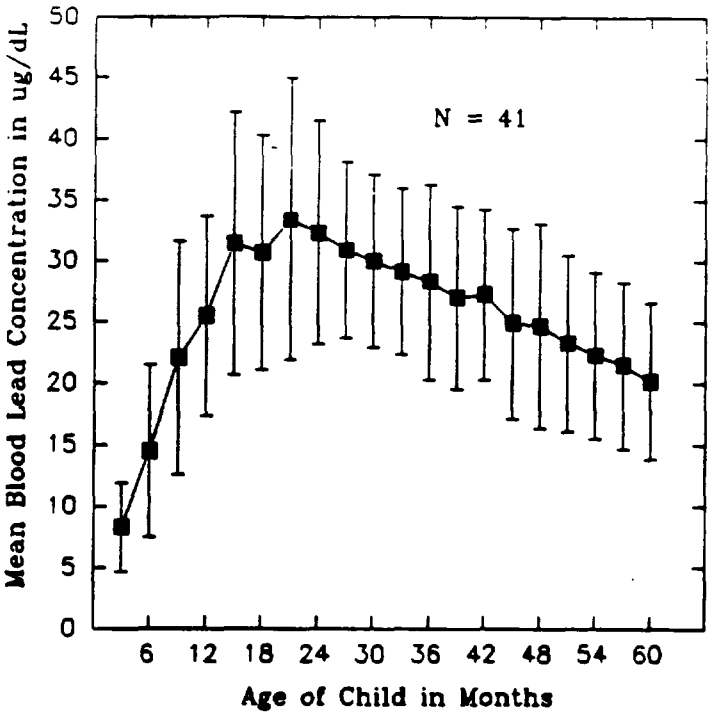

FIG. 3. Arithmetic mean (±SD) PbB concentrations from 3 to 60 months of age for subjects with average lifetime PbB concentrations greater than 20 μg/dL.

precision of measurement which is gained when testing the older child (9). This conclusion is further supported by the results of comprehensive neuromotor examinations conducted on this cohort at a later age. When subjects were assessed at 6 years, statistically significant, inverse relationships were found between prenatal and postnatal PbB concentrations and gross and fine-motor skills (10). The late results of the Cincinnati Prospective study provide essential confirmation of the findings reported out of Boston (2) and Port Pirie, South Australia (16,17), as well as support recent initiatives in the United States to reduce environmental lead exposure in children (24).

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